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Request for grant of a Patent

Form 1/77

Patents Act 1977

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1 Title of invention

1 Please give the title of the invention

COMPOUNDS USEFUL IN THERAPY

2 Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

2 Applicant's details

First or only applicant

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*

UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

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Forenames

2c **In all cases,** please give the following details:

Address
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Country UNITED KINGDOM

ADP number
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3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ ***go to 3b***

⬇ ***Please give details below***

Agent's name
DR. A.J. RUDGE

Agent's address
PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT

Postcode CT13 9NJ

Agent's ADP number 7936677001

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4 Referenc number

4 Agent's or applicant's reference number *(if applicable)* PCS10927AJR-PROV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes [ ] No [X] ➡ ***go to 6***

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6
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8
Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	8	Description	55
Abstract		Drawing(s)	

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8b Which of the following documents also accompanies the application?

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

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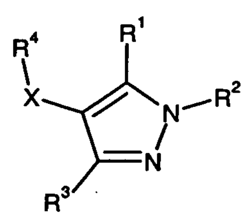
COMPOUNDS USEFUL IN THERAPY

This invention relates to compounds useful in the treatment or prevention of a variety of disorders, including those in which the inhibition of reverse transcriptase is important, and to compositions containing, the uses of, methods for the preparation of and intermediates used in the preparation of such compounds. Disorders of interest include those caused by Human Immunodificiency Virus (HIV) and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome (AIDS).

Without being limited by theory, the compounds of the present invention may bind to the enzyme reverse transcriptase and be modulators, especially inhibitors thereof. Reverse transcriptase is implicated in the infectious lifecycle of HIV, and compounds which interfere with the function of this enzyme have shown utility in the treatment of conditions including AIDS. There is a constant need to provide new and better modulators, especially inhibitors, of HIV reverse transcriptase since the virus is able to mutate, becoming resistant to their effects.

European patent application EP 0 786 455 A1 discloses a class of imidazole compounds which inhibit the growth of HIV. A class of N-phenylpyrazoles which act as reverse transcriptase inhibitors are disclosed in *J. Med. Chem.*, 2000, **43**, 1034.

According to the present invention there is provided a compound of the formula



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, $-OR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$,

$-NR^5CONR^6R^7$, $-NR^5SO_2R^6$ or R^8, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by halo, $-OR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$, $-NR^5CONR^6R^7$, $-NR^5SO_2R^6$ or R^8;

R^2 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl or C-linked R^{12}, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by $-OR^9$, $-CO_2R^9$, $-CO_2NR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{10}$ or R^{12};

R^3 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16}, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16};

R^4 is phenyl or pyridyl, each being optionally substituted by halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy;

R^5, R^6, R^7, R^9, R^{10}, R^{11}, R^{13}, R^{14} and R^{15} are either each H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl or, when two such groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached may represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

R^8, R^{12} and R^{16} are each a five- or six-membered heterocyclic group containing 1 to 4 heteroatoms selected from O, N and S and optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or halo; and

X is $-CH_2-$, $-S-$, $-SO-$ or $-SO_2-$.

In the above definitions, halo means fluoro, chloro, bromo or iodo. Alkyl and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, para-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge *et al*, *J. Pharm. Sci.*, **66**, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs, tautomers and radiolabelled forms thereof.

A compound of the formula (I) may contain one or more asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) together with mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or high performance liquid chromatography (HPLC) of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by HPLC of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Preferably, R^1 is C_1-C_6 alkyl optionally substituted by halo, $-OR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$, $-NR^5CONR^6R^7$, $-NR^5SO_2R^6$ or R^8 wherein R^5, R^6, R^7 and R^8 are as defined above.
More preferably, R^1 is C_1-C_6 alkyl.
Even more preferably, R^1 is C_1-C_3 alkyl.
Most preferably, R^1 is methyl, ethyl or prop-2-yl.

Preferably, R^2 is H or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by $-OR^9$, $-CO_2R^9$, $-CO_2NR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{10}$ or R^{12} wherein R^9, R^{10}, R^{11} and R^{12} are as defined above.
More preferably, R^2 is H, methyl or ethyl, said methyl or ethyl being optionally substituted by OR^9 or CO_2R^9 wherein R^9 is as defined above.
Even more preferably, R^2 is H, methyl or ethyl, said methyl or ethyl being optionally substituted by OH or $-CO_2CH_2CH_3$.
Most preferably, R^2 is H, $-CH_2CH_2OH$ or $-CH_2CO_2CH_2CH_3$.

Preferably, R^3 is C_1-C_6 alkyl optionally substituted by halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16} wherein R^{13}, R^{14}, R^{15} and R^{16} are as defined above.
More preferably, R^3 is C_1-C_3 alkyl optionally substituted by halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$,

$-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16} wherein R^{13}, R^{14}, R^{15} and R^{16} are as defined above.
Even more preferably, R^3 is methyl, ethyl or prop-2-yl, each optionally substituted by halo.
Most preferably, R^3 is methyl, ethyl, prop-2-yl or trifluoromethyl.

Preferably, R^4 is phenyl optionally substituted by halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy.
More preferably, R^4 is phenyl optionally substituted by halo.
Even more preferably, R^4 is phenyl optionally substituted by chloro or fluoro.
Most preferably, R^4 is 3-chlorophenyl, 3,5-dichlorophenyl, 3-fluorophenyl, 3,5-difluorophenyl or 4-chlorophenyl.

Preferably, X is $-CH_2-$ or -S-.
More preferably, X is $-CH_2-$.

Preferably, R^8, R^{12} and R^{16} are each imidazolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridonyl, triazinyl or pyrimidinyl, said imidazolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridonyl, triazinyl or pyrimidinyl being optionally substituted by C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, oxo or amino.

Particularly preferred individual compounds according to the invention include:

2-[4-(3,5-dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol; and
2-[4-(3,5-dichlorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol.

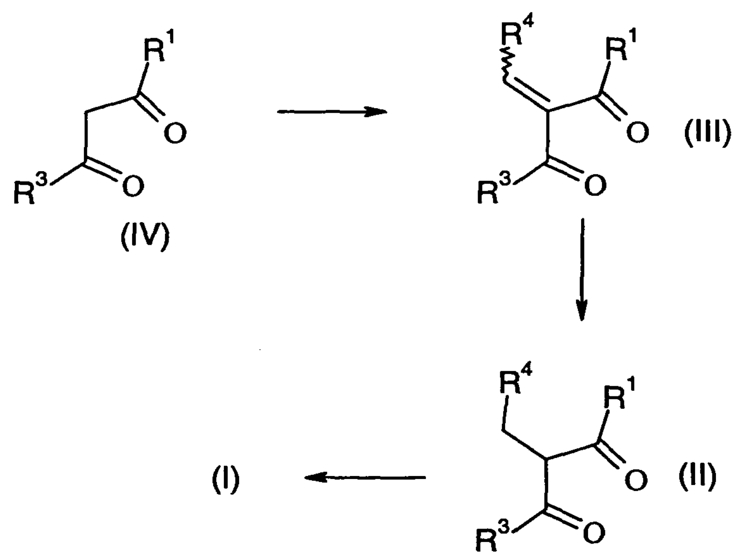
All of the compounds of the formula (I) can be prepared by conventional routes such as by the procedures described in the general methods presented below or by the specific methods described in the Examples section, or by similar methods thereto. The present invention also encompasses any one or more of these processes for

preparing the compounds of formula (I), in addition to any novel intermediates used therein.

In the following general methods, R^1, R^2, R^3, R^4 and X are as previously defined for a compound of the formula (I) unless otherwise stated.

Except where either R^1 or R^3 is halo, $-OR^5$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-NR^5CONR^6R^7$ or $-NR^5SO_2R^6$, compounds of the formula (I) in which X is $-CH_2-$ may be prepared using the route shown in Scheme 1.

Scheme 1



In Scheme 1, compounds of the formula (I) in which X is $-CH_2-$ may be prepared by the condensation of a compound of the formula (II) with a compound of the formula

$$H_2NNHR^2 \text{ (V)},$$

or a salt thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (II) in a suitable solvent, such as ethanol, is treated with the compound of the formula (V), or the salt thereof, and, if used, the appropriate acid or base, at a temperature of from

room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

Thus, according to another aspect of the invention, there is provided a process for the preparation of a compound of the formula (I), as defined above, which includes the reaction of a compound of the formula (II), as defined above, with a compound of the formula (V), as defined above.

Compounds of the formula (II) may be prepared by the reduction of a compound of the formula (III) with a suitable reducing agent such as (a) hydrogen in the presence of a palladium catalyst, (b) diphenylsilane in the presence of a palladium catalyst and a zinc salt or (c) triethylsilane in the presence of an acid such as trifluoroacetic acid. In a typical procedure, a solution of the compound of the formula (III) in a suitable solvent, such as ethanol or a mixture of ethanol and ethyl acetate, under a hydrogen atmosphere, is treated with 5% w/w palladium on barium sulphate. In another typical procedure, a solution of the compound of the formula (III) in a suitable solvent, such as dichloromethane, is treated with diphenylsilane, tetrakis(triphenylphosphine)palladium (0) and zinc chloride. In a further typical example, a solution of the compound of the formula (III) in a suitable solvent, such as dichloromethane, is treated with triethylsilane and trifluoroacetic acid.

Compounds of the formula (III) may be prepared by the condensation of a compound of the formula (IV) with a compound of the formula

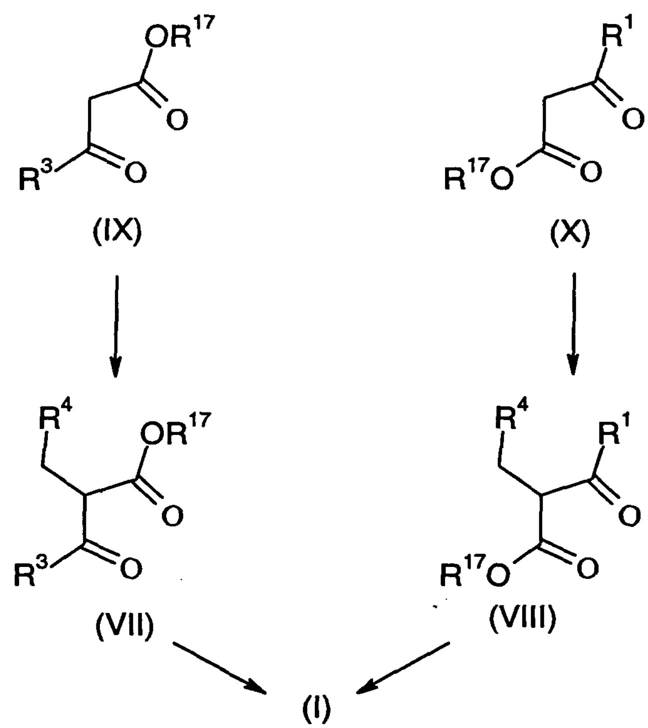
$$R^4CHO \text{ (VI)},$$

or a disguised form thereof, such as an acetal, optionally in the presence of a suitable catalyst, such as a mixture of acetic acid and piperidine. In a typical procedure, a solution of the compound of the formula (IV) in a suitable solvent such as toluene is treated with a compound of the formula (VI), acetic acid and piperidine and heated at a temperature of from room temperature to the reflux temperature of the solvent. Preferably, the reaction mixture is heated under reflux using a Dean-Stark apparatus. Compounds of the formula (III), prepared in this way, in which R^1

and R^3 are different, are usually formed as a mixture of stereoisomers. Such a mixture may be used directly in subsequent transformations or separated into its individual stereoisomers which may then be used separately.

Compounds of the formula (I) in which X is $-CH_2-$ and R^1 or R^3 is OH may be prepared using the route shown in Scheme 2.

Scheme 2



In Scheme 2, in which R^{17} is C_1-C_6 alkyl, compounds of the formula (I) in which X is $-CH_2-$ and R^1 is OH may be prepared by the reaction of a compound of the formula (VII) with a compound of the formula (V), or a salt thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (VII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (V), or the salt thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated

under reflux. The skilled man will appreciate that compounds of the formula (I) in which R^1 is OH may exist in one of several tautomeric forms.

Compounds of the formula (VII) may be prepared by the reaction of a compound of the formula (IX) with a compound of the formula

$$R^4CH_2Y \text{ (XI)}$$

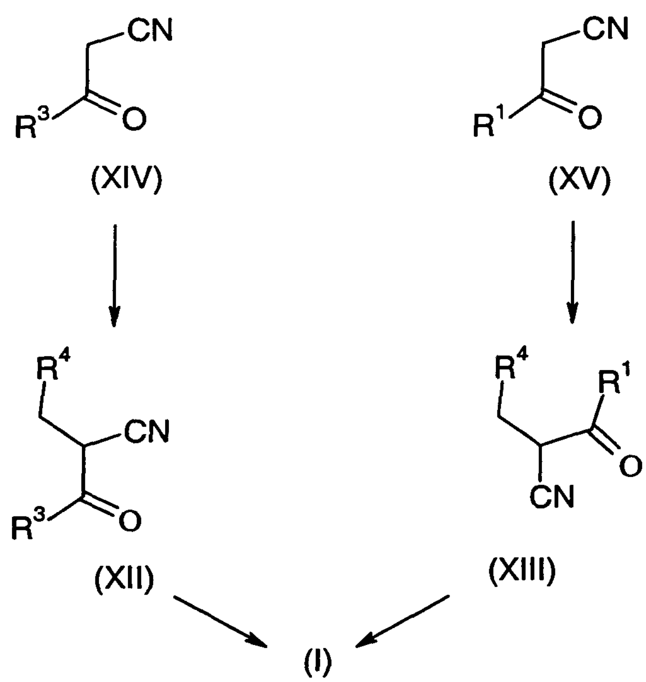
in which Y is chloro, bromo, iodo, $OSO_2(C_1\text{-}C_6$ alkyl) or OSO_2Ar, Ar being defined as phenyl or phenyl substituted by C_1-C_6 alkyl, in the presence of a suitable base. In a typical procedure, a solution of the compound of the formula (IX) in a suitable solvent, such as tetrahydrofuran, acetonitrile or diethylether, is treated with a base, such as sodium ethoxide or sodium carbonate, and the compound of the formula (XI), optionally with heating.

In Scheme 2, compounds of the formula (I) in which X is $-CH_2-$ and R^3 is OH may be prepared by the reaction of a compound of the formula (VIII) with a compound of the formula (V), or a salt thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (VIII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (V), or the salt thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux. The skilled man will appreciate that compounds of the formula (I) in which R^3 is OH may exist in one of several tautomeric forms.

Compounds of the formula (VIII) may be prepared by the reaction of a compound of the formula (X) with a compound of the formula (XI), in which Y is as defined above, in the presence of a suitable base. In a typical procedure, a solution of the compound of the formula (X) in a suitable solvent, such as tetrahydrofuran, acetonitrile or diethylether, is treated with a base, such as sodium ethoxide or sodium carbonate, and the compound of the formula (XI), optionally with heating.

Compounds of the formula (I) in which X is $-CH_2-$ and R^1 or R^3 is NH_2 may be prepared by the route shown in Scheme 3.

Scheme 3



In Scheme 3, compounds of the formula (I) in which X is $-CH_2-$ and R^1 is NH_2 may be prepared by the reaction of a compound of the formula (XII) with a compound of the formula (V), or a salt thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (XII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (V), or the salt thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

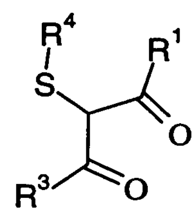
Compounds of the formula (XII) may be prepared by the reaction of a compound of the formula (XIV) with a compound of the formula (XI), in which Y is as defined above, in the presence of a suitable base. In a typical procedure, a solution of the

compound of the formula (XIV) in a suitable solvent, such as tetrahydrofuran, acetonitrile or diethylether, is treated with a base, such as sodium ethoxide or sodium carbonate, and the compound of the formula (XI), optionally with heating.

In Scheme 3, compounds of the formula (I) in which X is $-CH_2-$ and R^3 is NH_2 may be prepared by the reaction of a compound of the formula (XIII) with a compound of the formula (V), or a salt thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (XIII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (V), or the salt thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

Compounds of the formula (XIII) may be prepared by the reaction of a compound of the formula (XV) with a compound of the formula (XI), in which Y is as defined above, in the presence of a suitable base. In a typical procedure, a solution of the compound of the formula (XV) in a suitable solvent, such as tetrahydrofuran, acetonitrile or diethylether, is treated with a base, such as sodium ethoxide or sodium carbonate, and the compound of the formula (XI), optionally with heating.

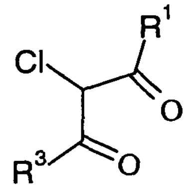
Compounds of the formula (I) in which X is S may be prepared by similar methods to those described above except that, for example, a compound of the formula



(XVI)

is substituted for a compound of the formula (II).

Compounds of the formula (XVI) are either commercially available or may be prepared by the reaction of a compound of the formula



(XVII)

with a compound of the formula

R^4SH (XVIII).

In a typical procedure a solution of a compound of the formula (XVII) in a suitable solvent, such as acetone, is treated with a compound of the formula (XVIII), optionally treated with a base, such as potassium carbonate and optionally treated with a catalyst such as sodium iodide or tributylammonium iodide. The reaction is preferably performed at room temperature.

Compounds of the formula (XVII) may be prepared by the reaction of a compound of the formula (IV) with a chlorinating agent such as sulphonyl chloride. In a typical procedure, the compound of the formula (IV) is treated with sulphonyl chloride, optionally in the presence of a suitable solvent such as dichloromethane.

It will be appreciated by those skilled in the art that, in many cases, compounds of the formula (I) may be converted into other compounds of the formula (I) by functional group transformations. For instance:

(a) Compounds of the formula (I) in which R^2 is H may be converted into compounds of the formula (I) in which R^2 is optionally substituted C_1-C_6 alkyl by reaction with an appropriate alkylating agent. In a typical procedure, a solution of a compound of the formula (I) in which R^2 is H in a suitable solvent such as ethanol is treated with an alkyl bromide, optionally treated with a base such as sodium ethoxide and heated at a temperature of from room temperature to the reflux temperature of the solvent.

(b) Compounds of the formula (I) in which R^2 contains as ester functionality may be reduced with a suitable reducing agent, such as lithium aluminium hydride, to give corresponding compounds of the formula (I) in which R^2 contains a hydroxy group. In a typical procedure, a solution of the compound of the formula (I), in which R^2 contains an ester group, in a suitable solvent, such as diethyl ether, is treated with lithium aluminium hydride, preferably with cooling to a temperature of from -78 °C to 0 °C.

(c) Compounds of the formula (I) in which R^1 or R^3 is OH may be alkylated with a compound of the formula

$$R^{18}Y \text{ (XIX)}$$

wherein Y is as defined above and R^{18} is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, optionally in the presence of a suitable base, to give compounds of the formula (I) in which R^1 or R^3, respectively, is O(C_1-C_6 alkyl) or O(C_3-C_8 cycloalkyl). In a typical procedure, a solution of the compound of the formula (I) in which R^1 or R^3 is OH in a suitable solvent, such as tetrahydrofuran, dimethylformamide or ethanol, is treated with a base, such as sodium ethoxide or sodium carbonate, and the compound of the formula (XIX), optionally with heating.

(d) Compounds of the formula (I) in which R^1 or R^3 are OH may be acylated with an isocyanate to give compounds of the formula (I) in which R^1 or R^3, respectively, is $OCONR^5R^6$ or $OCONR^{13}R^{14}$. In a typical procedure, a solution of the compound of the formula (I) in which R^1 or R^3 is OH in a suitable solvent, such as dichloromethane, is treated with the isocyanate.

(e) Compounds of the formula (I) in which R^1 or R^3 is OH may be converted into compounds of the formula (I) in which R^1 or R^3, respectively, is halo by reaction with a suitable halogenating agent. In a typical procedure, the compound of the formula (I) in which R^1 or R^3 is OH is treated with $POCl_3$, optionally in the presence of a suitable solvent such as dimethylformamide, to give a compound of the formula (I) in which R^1 or R^3, respectively, is chloro.

(f) Compounds of the formula (I) in which R^1 or R^3 is NH_2, may be converted into compounds of the formula (I) in which R^1 or R^3, respectively, is NHR^{19}, where R^{19} is C_1-C_6 alkyl or C_3-C_8 cycloalkyl by an alkylation reaction of the type described in (c) above or a reductive amination with an appropriate aldehyde or ketone. In a typical reductive amination, the reaction will proceed in a suitable solvent such as dichloromethane, in the presence of a suitable reducing agent such as sodium triacetoxyborohydride and optionally in the presence of an acid such as acetic acid. A further alkylation or reductive amination may be performed on a compound of the formula (I) in which R^1 or R^3 is NHR^{19} to give a compound of the formula (I) in which R^1 or R^3, respectively, is $NR^{19}R^{20}$, where R^{19} is as defined above and R^{20} is defined in the same way as R^{19}.

(g) Compounds of the formula (I) in which R^1 or R^3 is NH_2, may be converted into compounds of the formula (I) in which, respectively, R^1 is NR^5COR^6, $NR^5CONR^6R^7$, $NR^5CO_2R^6$ or $NR^5SO_2R^6$ or R^3 is $NR^{13}COR^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}CO_2R^{14}$ or $NR^{13}SO_2R^{14}$ by reaction with an appropriate acylating or sulphonylating agent in a suitable inert solvent, such as dichloromethane, optionally in the presence of a base, preferably a tertiary amine base such as triethylamine.

(h) Compounds of the formula (I) in which R^1 or R^3 is CO_2R^5, where R^5 is other than H, may be converted into compounds of the formula (I) in which R^1 or R^3, respectively, is CO_2H by hydrolysis. Typically, the reaction will be carried out in a suitable solvent, such as water, ethanol or 1,4-dioxan or any combination thereof, and in the presence of a base such as sodium hydroxide.

(i) Compounds of the formula (I) in which R^1 or R^3 is CO_2H, may be converted into compounds of the formula (I) in which R^1 or R^3, respectively, is NH_2, by the Curtius rearrangement. In a typical procedure, the reaction is carried out in a suitable solvent, such as dichloromethane, in the presence of a reagent such as diphenylphosphoryl azide.

(j) Compounds of the formula (I) in which X is -S- may be converted into compounds of the formula (I) in which X is -SO- by reaction with a suitable oxidising agent, such as meta-chloroperoxybenzoic acid. The reaction is carried out in the presence of a suitable solvent such as dichloromethane.

(k) Compounds of the formula (I) in which X is -S- may be converted into compounds of the formula (I) in which X is $-SO_2-$ by reaction with a suitable oxidising agent such as oxone (trade mark) or hydrogen peroxide. In a typical procedure, a solution of the compound of the formula (I) in which X is -S- in a suitable solvent, such as acetic acid, is treated with hydrogen peroxide.

Compounds of the formula (IV), (V), (VI), (IX), (X), (XI), (XIV), (XV), (XVIII) and (XIX) are either commercially available or easily prepared by methods well known to those skilled in the art.

The compounds of the formula (I) and their pharmaceutically acceptable salts are useful because they have pharmacological activity in animals, including humans. More particularly, they are useful in the treatment or prevention of a disorder in which the inhibition of reverse transcriptase is important. Such disorders include those caused by Human Immunodificiency Virus (HIV) and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome, AIDS. The compounds of the formula (I), and their pharmaceutically acceptable salts may be administered alone or as part of a combination therapy.

Thus, according to a further aspect of the invention, there is provided a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use as a medicament.

According to a further aspect of the invention, there is provided the use of a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a disease treatable by the inhibition of reverse transcriptase.

According to a further aspect of the invention, there is provided the use of a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment or prevention of a retroviral infection.

According to a further aspect of the invention, there is provided the use of a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment or prevention of AIDS or HIV infection.

According to a further aspect of the invention, there is provided a method of treatment or prevention of a disorder treatable by the inhibition of reverse transcriptase, comprising the administration of an effective amount of a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need of such treatment or prevention.

According to a further aspect of the invention, there is provided a method of treatment or prevention of a retroviral infection, comprising the administration of an effective amount of a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need of such treatment or prevention.

According to a further aspect of the invention, there is provided a method of treatment or prevention of AIDS or HIV infection, comprising the administration of an effective amount of a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need of such treatment or prevention.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

Thus, according to another aspect of the invention there is provided a pharmaceutical composition containing a compound of the formula (I), as defined

above, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, sustained-, pulsed- or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or a high molecular weight polyethylene glycol. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol or glycerin, and combinations thereof.

The compounds of the formula (I) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily

accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will usually be from 0.01 to 30 mg/kg, preferably from 0.01 to 5 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 1 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion,

solution, cream, ointment or dusting powder. The compounds of the formula (I) may also be transdermally administered, for example, by the use of a skin patch.

For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the formula (I) may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Oral administration is preferred.

Included within the scope of the present invention are embodiments comprising the co-administration of a compound of the present invention with one or more additional therapeutic agents, and compositions containing a compound of the present invention along with one or more additional therapeutic agents. Such a

combination therapy is especially useful for the prevention and/or treatment of infection by HIV and related retroviruses which may evolve rapidly into strains resistant to any monotherapy. Alternatively, additional therapeutic agents may be desirable to treat diseases and conditions which result from or accompany the disease being treated with the compound of the present invention. For example, in the treatment of an HIV or related retroviral infection, it may be desirable to additionally treat opportunistic infections, neoplasms and other conditions which occur as a result of the immuno-compromised state of the patient being treated.

Preferred combinations of the present invention include simultaneous or sequential treatment with a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and:

(a) one or more reverse transcriptase inhibitors such as zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and adefovir;
(b) one or more non-nucleoside reverse transcriptase inhibitors such as nevirapine, delavirdine and efavirenz;
(c) one or more HIV protease inhibitors such as indanivir, ritonavir, saquinavir and nelfinavir;
(d) one or more CCR5 antagonists such as TAK-779;
(e) one or more CXCR4 antagonists such as AMD-3100;
(f) one or more integrase inhibitors;
(g) one or more inhibitors of viral fusion such as T-20;
(h) one or more investigational drugs such as trizivir, KNI-272, amprenavir, GW-33908, FTC, PMPA, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378 and KNI-764; or
(i) one or more antifungal or antibacterial agents such as fluconazole.

The activity of the compounds of the invention as reverse transcriptase inhibitors and as agents for treating HIV infections may be measured using the following assays.

A. Inhibition of HIV-1 reverse transcriptase enzyme

The reverse transcriptase activity of the compounds of the invention may be assayed as following. Using the purified recombinant HIV-1 reverse transcriptase (RT, EC, 2.7.7.49) obtained by expression in Escherichia Coli , a 96-well plate assay system was established for assaying a large number of samples using Poly r(A) Reverse Transcriptase [3H]-SPA enzyme assay system (Amersham NK9020) and following the manufacturer's recommendations. The compounds were dissolved in 100% DMSO and diluted with the buffer used in the Amersham assay system to a 5% final DMSO concentration. The inhibitory activity was expressed in percent inhibition relative to the DMSO control. The concentration at which the compound inhibited the reverse transcriptase by 50% was expressed as the IC_{50} of the compound.

B. Anti-Human Immunodeficiency Virus (HIV-1) cell culture assay

The anti-HIV activity of selected Examples of the invention was assayed by the following procedures.

1) SupT1 cells were cultured in an RPMI-1640 medium supplemented with 10% foetal calf serum and were split so that they were in growth phase on the day of use.

2) The compounds were dissolved in 100% DMSO and diluted with the above culture medium to predetermined concentrations and distributed in 20µl aliquots into a 96-well microtiter plate (0.1% DMSO final concentration).

3) To prepare infected cells, 100µl of RF viruses (TCID50 of 10^7/ml) were added to 10^6 cells and incubated for 1 hour at 37°C. The cells were then washed twice in PBS and resuspended in the culture medium at a density of 2.2 $\times 10^5$cells/mL. 180µl of these infected cells was transferred to wells of the 96 well plate containing the compounds.

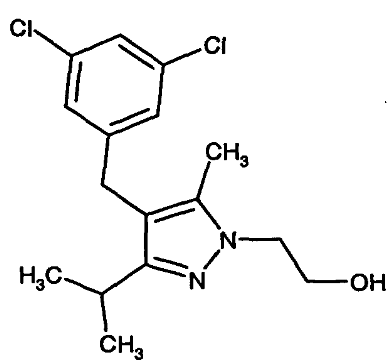
4) The plate was incubated in a CO_2 incubator at 37°C for 4 days. The cell survival rates were measured following the manufacturer's recommendations (CellTiter 96® AQ_{ueous} Non-Radioactive Assay - Promega (cat no: G5430)). The concentration at which the compound inhibited the cytotoxic effect of the virus by 50% was expressed as the EC_{50}.

The following Examples 1-19 illustrate the preparation of the compounds of the formula (I). The synthesis of certain intermediates used therein are described in the Preparations section that follows the Examples.

^1H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used: HRMS, high resolution mass spectrometry; hplc, high performance liquid chromatography; nOe, nuclear Overhauser effect; m.p., melting point; $CDCl_3$, deuterochloroform; D_6-DMSO, deuterodimethylsulphoxide; CD_3OD, deuteromethanol. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F_{254} plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. In certain of the examples (7, 9, 12 and 14) there is the possibility of regioisomerism in the product. The structures of Examples 7 and 12 have been proven by nOe experiments. The regiochemistry of Examples 9 and 14 has been assigned by comparing characteristic shifts in their NMR spectra with the corresponding shifts in the NMR spectra of Examples 7 and 12.

EXAMPLE 1

2-[4-(3,5-Dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol



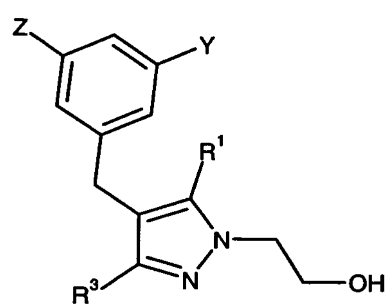
A solution of the ester of Example 7 (170mg, 0.46mmol) in dry ether (3.5mL) was added to a suspension of lithium aluminium hydride (17.5mg, 0.46mmol) in dry ether

(2mL) cooled to -78°C under nitrogen. After stirring at -78°C for 1hour and at 0°C for 1hour the reaction was quenched with water (5mL) and then partitioned between ether (30mL) and aqueous hydrochloric acid solution pH= 3 (30mL) and the aqueous layer was further extracted with ether (2x30mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to provide the title compound (116.3mg) as a white solid, m.p. 77-78°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.18 (d, 6H), 2.08 (s, 3H), 2.80 (heptet, 1H), 3.75 (s, 2H), 4.00 (m, 2H), 4.06 (m, 2H), 4.19 (t, 1H), 6.97 (s, 2H), 7.18 (s, 1H).
HRMS (electrospray): m/z [MH^+] 327.1026 (calculated 327.1026).

EXAMPLES 2 to 6

The compounds of the following tabulated examples of the general formula:



were prepared by a similar method to that of Example 1 using the appropriate esters.

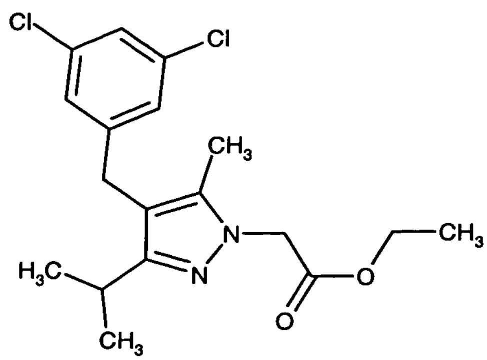
Example No.	R^3	R^1	Z	Y	LRMS m/z =	Analytical data, starting ester and variations in procedure.
2	CH_3CH_2-	CH_3CH_2-	Cl	Cl	(thermospray): 327 [MH^+]	^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.06 (t, 3H), 1.18 (t, 3H), 2.50 (m, 4H), 3.72 (s, 2H), 4.05 (m, 2H), 4.12 (m, 2H), 4.19 (br. t, 1H), 6.99 (s, 2H), 7.19 (s, 1H). Contains *ca.* 10% monodechlorinated impurity as judged by LCMS (50x2mm Magellen 3 micron C18 column, solvent gradient 0.1%, by volume aqueous formic acid:0.1%, by volume formic acid in acetonitrile (95:5, by volume) to 0.1%, by volume aqueous formic acid:0.1%, by volume formic acid in acetonitrile (5:95, by volume), electrospray MS). Ester from Example 8. Chromatography with a solvent gradient of toluene:ethyl acetate (1:1, by volume) then toluene:ethyl acetate (1:2, by volume).
3	$CH_3CH(CH_3)$-	CH_3-	Cl	H	(thermospray): 293 [MH^+]	^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (d, 6H), 2.06 (s, 3H), 2.82 (m, 1H), 3.73 (s, 2H), 3.99 (m, 2H), 4.06 (m, 2H), 4.29 (br. s, 1H), 6.96 (m, 1H), 7.05 (s, 1H), 7.15 (m, 2H).

						Microanalysis: Found: C, 65.58; H, 7.30; N, 9.33. $C_{16}H_{21}ClN_2O$ requires C, 65.63; H, 7.23; N, 9.57%. Ester from Example 14. Chromatography with a solvent gradient of pentane:ethyl acetate (2:1, by volume) then pentane:ethyl acetate (1:1, by volume).
4	$CH_3CH(CH_3)$-	CH_3-	F	F	(electrospray): 295 [MH^+]	^1H-NMR (400MHz, $CDCl_3$): δ = 1.10 (d, 6H), 2.10 (s, 3H), 2.80 (heptet, 1H), 3.74 (s, 2H), 4.00 (m, 2H), 4.06 (m, 2H), 4.20 (t, 1H), 6.60 (m, 3H). Ester from Example 15. Chromatography with a solvent gradient of pentane:ethyl acetate (2:1, by volume) then pentane:ethyl acetate (1:1, by volume).
5	$CH_3CH(CH_3)$-	CH_3-	F	H	(thermospray): 277 [MH^+]	^1H-NMR (400MHz, $CDCl_3$): δ = 1.18 (d, 6H), 2.08 (s, 3H), 2.84 (heptet, 1H), 3.76 (s, 2H), 3.98 (m, 2H), 4.05 (m, 2H), 4.23 (t, 1H), 6.75 (d, 1H), 6.86 (m, 2H), 7.20 (m, 1H). Microanalysis: Found: C, 69.45; H, 7.71; N, 9.96. $C_{16}H_{21}FN_2O$ requires C, 69.54; H, 7.66; N, 10.14%. Ester from Example 9. Chromatography with pentane:ethyl acetate (1:1, by

						volume).
6	CH_3-	$CH_3CH(CH_3)$-	Cl	Cl	(thermospray): 327 $[MH^+]$	^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (d, 6H), 2.06 (s, 3H), 3.06 (heptet,1H), 3.79 (s, 2H), 4.00 (m, 2H), 4.13 (m, 2H), 6.95 (s, 2H), 7.18 (s, 1H). HRMS (electrospray): m/z $[MH^+]$ 327.1031 (calculated 327.1026). Ester from Example 7, Method B, second product. Chromatography with a solvent gradient of pentane:ethyl acetate (1:1, by volume) then ethyl acetate.

EXAMPLE 7

Ethyl [4-(3,5-dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate



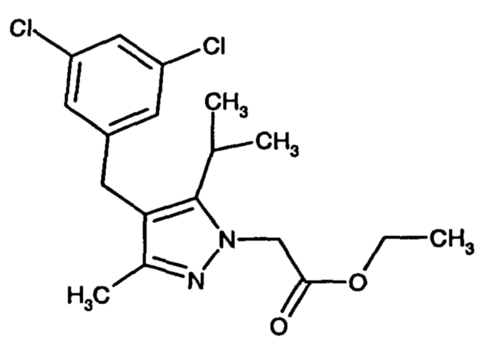
Method A:

A solution of 21% weight/volume sodium ethoxide in ethanol (227μL, 0.7mmol) was added dropwise to a stirred solution of the pyrazole from Example 16 (172.7mg, 0.61mmol) in dry ethanol (1mL) at room temperature in a Reacti-vial™ (a sealable reaction vessel; available from Pierce & Warriner (UK) Ltd). Ethyl bromoacetate (136μL, 1.22mmol) was added and the Reacti-vial™ was sealed and heated at 80°C for 2 hours and then stirred at room temperature for 16 hours. Further sodium ethoxide in ethanol (227μL, 0.7mmol) and ethyl bromoacetate (136μL, 1.22mmol) were added and the sealed mixture was heated for a further 7 hours. After cooling to room temperature further sodium ethoxide in ethanol (227μL, 0.7mmol) and ethyl bromoacetate (136μL, 1.22mmol) were added and the sealed mixture was heated for a further 10 hours. After cooling to room temperature the mixture was concentrated under reduced pressure and the residue was partitioned between water (30mL) and dichloromethane (30mL) and the aqueous layer was further extracted with dichloromethane (2x30mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure and the crude product (321mg) was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (7:1, by volume) to provide the title compound (175.3mg) as a white solid, m.p. 90-92°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.18 (d, 6H), 1.27 (t, 3H), 2.06 (s, 3H), 2.81 (heptet, 1H), 3.74 (s, 2H), 4.22 (q, 2H), 4.83 (s, 2H), 6.96 (s, 2H), 7.17 (s, 1H). This structure was confirmed by nOe experiments.
HRMS (electrospray): m/z [MH^+] 369.1135 (calculated 369.1131).

Method B:
A solution of the β-diketone from Preparation 1 (245mg, 0.85mmol), ethyl hydrazinoacetate hydrochloride (132mg, 0.85mmol) and triethylamine (131µL, 0.94mmol) in ethanol (1mL) was stirred and heated in a sealed Reacti-vial™ at 80°C for 24 hours. After cooling the mixture was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (10:1, by volume) then pentane:ethyl acetate (5:1, by volume) to provide the title compound (28.6mg) as a white solid, m.p. 94-95°C.

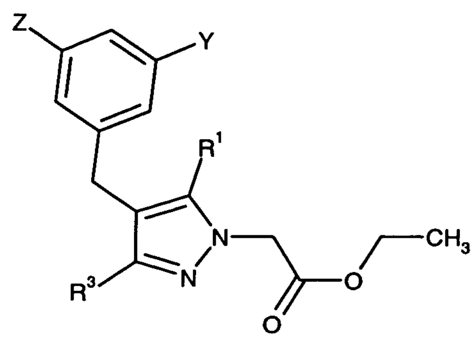
Further elution of the column afforded a second product ethyl [4-(3,5-dichlorobenzyl)-5-isopropyl-3-methyl-1*H*-pyrazol-1-yl]acetate (228.8mg) as a yellow oil.



^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.19 (d, 6H), 1.28 (t, 3H), 2.06 (s, 3H), 2.92 (heptet, 1H), 3.82 (s, 2H), 4.23 (q, 2H), 4.86 (s, 2H), 6.96 (s, 2H), 7.17 (s, 1H). This structure was confirmed by nOe experiments.
HRMS (electrospray): m/z [MH^+] 369.1134 (calculated 369.1131).

EXAMPLES 8 to 9

The compounds of the following tabulated Examples of the general formula:



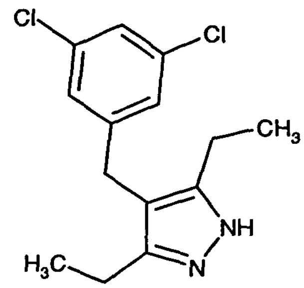
were prepared by a similar method to that of Example 7, Method A using the appropriate pyrazole.

Example No.	R^3	R^1	Z	Y	LRMS m/z =	Analytical data, starting pyrazole and variations in procedure.
8	CH_3CH_2-	CH_3CH_2-	Cl	Cl	(thermospray): 369 [MH^+]	^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.14 (t, 3H), 1.16 (t, 3H), 1.28 (t, 3H), 2.48 (m, 4H), 3.75 (s, 2H), 4.24 (q, 2H), 4.84 (s, 2H), 6.99 (s, 2H), 7.19 (s, 1H). Pyrazole from Example 10. Microanalysis: Found: C, 58.41; H, 5.95; N, 7.39. $C_{18}H_{22}Cl_2N_2O_2$ requires C, 58.54; H, 6.00; N, 7.59%. Contains *ca.* 10% monodechlorinated impurity as judged by LCMS. Chromatography with a solvent gradient of dichloromethane then dichloromethane:methanol (99:1, by volume).
9	$CH_3CH(CH_3)$-	CH_3-	F	H	(thermospray): 319 [MH^+]	^{1}H-NMR (400MHz, $CDCl_3$): δ =1.13 (d, 6H), 1.23 (t, 3H), 2.03 (s, 3H), 2.80 (heptet, 1H), 3.75 (s, 2H), 4.20 (q, 2H), 4.80 (s, 2H), 6.71 (d, 1H), 6.85 (m, 2H), 7.16 (m, 1H). HRMS (electrospray): m/z [MH^+] 319.1814 (calculated 319.1817).

						Pyrazole from Example 18. Chromatography with pentane:ethyl acetate (5:1, by volume).

EXAMPLE 10

4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazole



Hydrazine hydrate (187µL, 3.85mmol) was added to a stirred solution of the β-diketone from Preparation 5 (1.00g, 3.5mmol) in ethanol (2.5mL) in a Reacti-vial™ at room temperature. The Reacti-vial™ was sealed and the mixture heated at 100°C for 3 hours. After cooling to room temperature the mixture was concentrated under reduced pressure to leave an oily white solid (1g) which was purified by flash chromatography on silica gel eluting with dichlormethane:methanol (98:2, by volume) to give the crude product which was recrystallised from diisopropylether (10mL) to give the title compound (150mg) as a white solid. LCMS analysis revealed a small amount (*ca.*10%) of monodechlorinated impurity carried through from Preparation 5. This impurity could be removed by hplc (150x21.2mm Phenomenonex Luna C_{18} 5 micron column, solvent gradient 0.1%,by volume aqueous diethylamine:methanol (90:10, by volume) to 0.1%,by volume aqueous diethylamine:methanol (10:90, by volume)) to afford pure title compound.

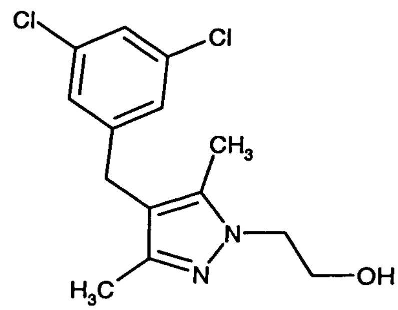
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.20 (t, 6H), 2.55 (q, 4H), 3.73 (s, 2H), 6.99 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MH^+] 283.

Microanalysis: Found: C, 59.53; H, 5.71; N, 9.82. $C_{14}H_{16}Cl_2N_2$ requires C, 59.38; H, 5.69; N, 9.89%.

EXAMPLE 11

2-[4-(3,5-Dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanol



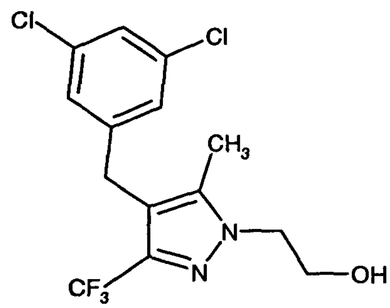
To a stirred suspension of the diketone from Preparation 4 (302mg, 1.17mmol) in ethanol (1mL) was added 2-hydroxyethyl hydrazine (81μL, 1.29mmol) and the resulting mixture was heated at 100°C in a sealed Reacti-vial™ for 6 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (1:2, by volume) then pentane:ethyl acetate (1:5, by volume) to afford the title compound (351mg) as a white powder.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.11 (s, 3H), 3.62 (br. m, 1H), 3.66 (s, 2H), 4.00 (m, 2H), 4.07 (m, 2H), 6.95 (s, 2H), 7.16 (s, 1H).
LRMS (thermospray): m/z [MH^+] 299.
Microanalysis: Found: C, 56.15; H, 5.38; N, 9.27. $C_{14}H_{16}Cl_2N_2O$ requires C, 56.20; H, 5.39; N, 9.36%.

LCMS analysis revealed a small amount (<10%) of dechlorinated impurities presumably arising from the reduction step in Preparation 6 but not detected at that stage. A portion of the product (190mg) was recrystallised from ethanol:water (2:1, by volume) (3mL) to afford a white solid (150mg). LCMS analysis then revealed only a trace amount (<5%) of mono-chlorinated product. This over reduction could probably be avoided by using the alternative reduction procedure of Preparation 6.

EXAMPLE 12

2-[4-(3,5-Dichlorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol



A solution of the diketone from Preparation 6 (76mg, 0.243mmol) in ethanol (2mL) was added to 2-hydroxethyl hydrazine (18µL, 0.267mmol) and the resulting mixture was heated at 90°C in a sealed Reacti-vial™ for 2 hours. After cooling the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane then dichloromethane:methanol (99:1, by volume) to afford the title compound (62mg) as an off-white solid, m.p. 91-93°C.

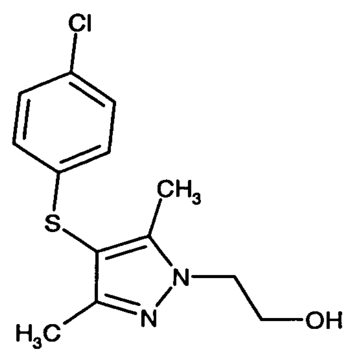
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.61 (m, 1H), 3.80 (s, 2H), 4.05 (m, 2H), 4.17 (m, 2H), 6.92 (s, 2H), 7.16 (s, 1H). This structure was confirmed by nOe experiments.

LRMS (thermospray): m/z [MH^+] 353.

Microanalysis: Found: C, 47.66; H, 3.75; N, 7.78. $C_{14}H_{13}Cl_2F_3N_2O$ requires C, 47.61; H, 3.71; N, 7.93%.

EXAMPLE 13

2-{4-[(4-Chlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol



The title compound was prepared by a similar method to that of Example 12 using 3-(4-chlorophenylthio)pentane-2,4-dione except that the crude product was purified by recrystallisation from diisopropylether (*ca.* 25mL) to give pale yellow crystals, m.p. 88.9-90.3°C

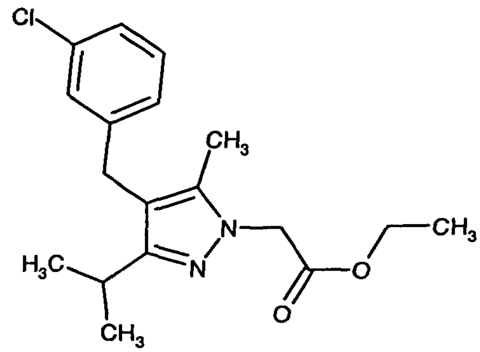
^{1}H-NMR 300MHz, $CDCl_3$): δ = 2.20 (s, 3H), 2.29 (s, 3H), 4.04 (t, 2H), 4.12 (t, 2H), 6.90 (d, 2H), 7.18 (d, 2H).

LRMS (thermospray): m/z [MH^+] 282.

Microanalysis: Found: C, 54.92; H, 5.39; N, 9.91. $C_{13}H_{15}ClN_2OS$ requires C, 55.22; H, 5.35; N, 9.91%.

EXAMPLE 14

Ethyl [4-(3-chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate



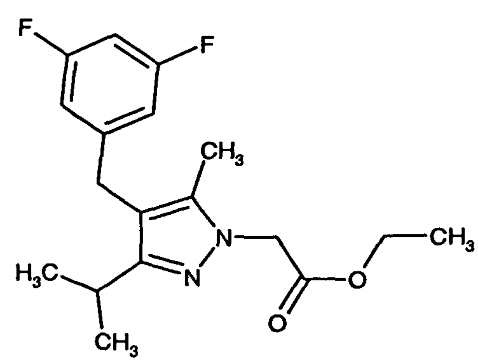
The title compound was prepared by a method similar to that of Example 7, Method A using the pyrazole of Example 19, and was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (5:1, by volume) and was obtained as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (d, 6H), 1.26 (t, 3H), 2.03 (s, 3H), 2.79 (m, 1H), 3.72 (s, 2H), 4.19 (q, 2H), 4.81 (s, 2H), 6.93 (m, 1H), 7.03 (s, 1H), 7.11 (m, 2H).

LRMS (thermospray): m/z [MH^+] 335.

EXAMPLE 15

Ethyl [4-(3-chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate

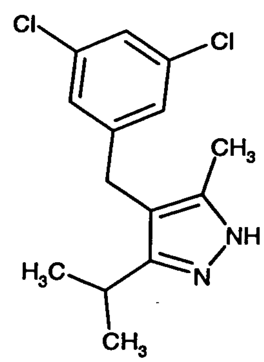


The title compound was prepared by a method similar to that of Example 7, Method A using the pyrazole of Example 17 and was obtained as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (d, 6H), 1.27 (t, 3H), 2.06 (s, 3H), 2.82 (heptet, 1H), 3.76 (s, 2H), 4.23 (q, 2H), 4.84 (s, 2H), 6.60 (m, 3H).
HRMS (electrospray): m/z [MH^+] 337.1719 (calculated 337.1722).

EXAMPLE 16

4-(3,5-Dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole

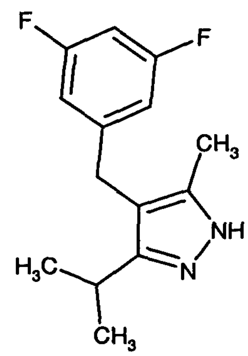


Hydrazine hydrate (50.1mg, 1mmol) was added dropwise to a stirred solution of the β-diketone from Preparation 1 (287.2mg, 1mmol) in dry ethanol (1mL) in a Reacti-vial™ at RT. The Reacti-vial™ was sealed and the mixture heated at 80°C for 24 hours. After cooling to room temperature the mixture was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (3:1, by volume) then pentane:ethyl acetate (2:1, by volume) to afford the title compound (225.6mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (d, 6H), 2.11 (s, 3H), 2.89 (heptet, 1H), 3.74 (s, 2H), 6.97 (s, 2H), 7.18 (s, 1H).
LRMS (electrospray): m/z [MH^+] 285.

EXAMPLE 17

4-(3,5-Difluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole

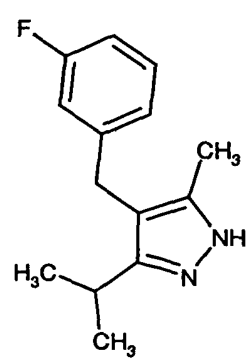


The title compound was prepared by a method similar to that of Example 16 using the β-diketone from Preparation 2 and was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to afford the title compound as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (d, 6H), 2.08 (s, 3H), 2.85 (heptet, 1H), 3.71 (s, 2H), 6.58 (m, 3H).
LRMS (thermospray): m/z [MH^+] 251.

EXAMPLE 18

4-(3-Fluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole

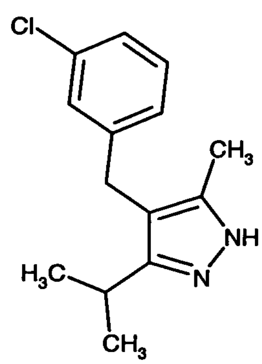


The title compound was prepared by a method similar to that of Example 16 using the β-diketone from Preparation 3 and was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (3:1, by volume) then pentane:ethyl acetate (2:1, by volume) to afford the title compound as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.22 (d, 6H), 2.11 (s, 3H), 2.90 (heptet, 1H), 3.77 (s, 2H), 6.77 (d, 1H), 6.89 (m, 2H), 7.20 (m, 1H).
LRMS (thermospray): m/z [MH^+] 233.

EXAMPLE 19

4-(3-Chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole



The title compound was prepared by a method similar to that of Example 10 using the β-diketone of Preparation 7 and was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (5:1, by volume) then pentane:ethyl acetate (3:1, by volume) to afford the title compound as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.19 (d, 6H), 2.10 (s, 3H), 2.84-2.97 (m, 1H), 3.74 (s, 2H), 6.94-6.99 (m, 1H), 7.06 (s, 1H), 7.11-7.21 (m, 2H).
LRMS (thermospray): m/z [MH^+] 249.

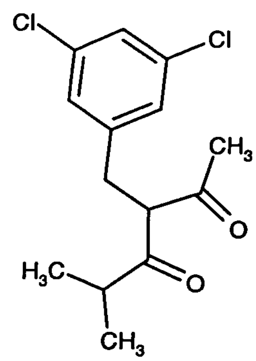
EXAMPLE 20

The compounds of Examples 1-13 and Example 16 were tested in assay A (inhibition of HIV-1 reverse transcriptase enzyme) described on page 21 and found to have an IC_{50} value of less than 100 μM.

The following Preparations describe the preparation of certain intermediates used in the preceding Examples 1-19.

PREPARATION 1

3-(3,5-Dichlorobenzyl)-5-methyl-2,4-hexanedione



Method A:

5% Palladium on barium sulphate (10mg) was added to a stirred solution of the more polar alkene isomer from Preparation 8 (100mg) in ethanol (2.5mL) and the resulting mixture was stirred under a 15psi pressure of hydrogen for 3 hours. The mixture was filtered through a filter aid (Arbocel^{TM})(caution - fire hazard) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (10:1, by volume) to give the title compound (72mg) as a 43:57mixture with its enol tautomer as estimated by ^{1}H-NMR as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (d, 6H, diketone and enol), 2.02 (s, 3H, enol), 2.11 (s, 3H, diketone), 2.52 (heptet, 1H, diketone), 2.61 (heptet, 1H, d, enol), 3.00 (dd, 1H, diketone), 3.06 (dd, 1H, diketone), 3.60 (s, 2H, enol), 4.00 (t, 1H, diketone), 6.98 and 7.00 (2s, 2x2H, diketone and enol), 7.18 (s, 1H, diketone and enol).

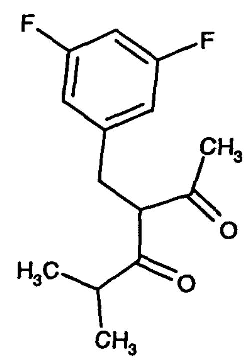
LRMS (thermospray): m/z [MH^+] 304.

Method B:

The less polar alkene isomer from Preparation 8 was reduced in the same way as for the more polar isomer in Method A above but stirring the mixture for 9 hours and flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) then pentane:ether (10:1, by volume) to give the title compound as a yellow oil.

PREPARATION 2

3-(3,5-Difluorobenzyl)-5-methyl-2,4-hexanedione



Method A:

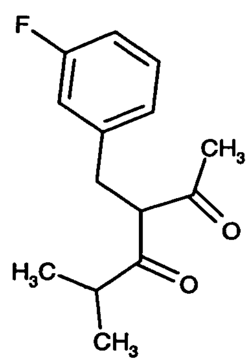
5% Palladium on barium sulphate (56mg) was added to a stirred solution of the more polar alkene isomer from Preparation 11 (560mg) in ethanol (16mL) and the resulting mixture was stirred under a 15psi pressure of hydrogen for 4 hours. The mixture was filtered through a filter aid (Arbocel™)(caution - fire hazard) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give the title compound (513.1mg) as a 35:65 mixture with its enol tautomer as estimated by ^{1}H-NMR as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (d, 6H, diketone and enol), 2.03 (s, 3H, enol), 2.13 (s, 3H, diketone), 2.55 (heptet, 1H, diketone), 2.65 (heptet, 1H, enol), 3.03 (dd, 1H, diketone), 3.11 (dd, 1H, diketone), 3.65 (s, 2H, enol), 4.03 (t, 1H, diketone), 6.65 (m, 3H, diketone and enol).
LRMS (electrospray): m/z [MNa^+] 277.

Method B:
The less polar alkene isomer from Preparation 11 was reduced in the same way as for the more polar isomer in Method A above but stirring the mixture for 25 hours to give the title compound as a yellow oil.

PREPARATION 3

3-(3-Fluorobenzyl)-5-methyl-2,4-hexanedione



The title compound was prepared by a method similar to that of Preparation 2 using the alkene isomers of Preparation 12 to give the title compound as a 38:62 mixture with its enol tautomer as estimated by ^{1}H-NMR as a yellow oil.

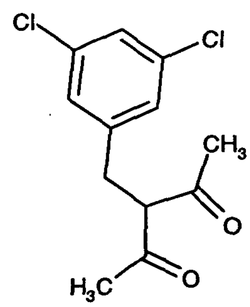
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.06 (d, 6H, diketone and enol), 2.06 (s, 3H, enol), 2.16 (s, 3H, diketone), 2.55 (heptet, 1H, diketone), 2.73 (heptet, 1H, enol), 3.08 (dd, 1H, diketone), 3.16 (dd, 1H, diketone), 3.68 (s, 2H, enol), 4.10

(t, 1H, diketone), 6.89 (m, 3H, diketone and enol), 7.27 (m, 1H, diketone and enol).

LRMS (electrospray): m/z [MNa^+] 259.

PREPARATION 4

3-(3,5-Dichlorobenzyl)-2,4-pentanedione



To a solution of the alkene from Preparation 9 (6.4g, 24.9mmol) in ethanol (100mL) and ethyl acetate (40mL) was added 5% palladium on barium sulphate (640mg) and the resulting mixture was stirred under a 15psi pressure of hydrogen for 18 hours. The mixture was filtered through a filter aid (Arbocel™)(caution - fire hazard) under nitrogen and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (10:1, by volume) then pentane:ethyl acetate (7:1, by volume) to give the title compound (5.3g) as a mixture with its enol tautomer as shown by ^{1}H-NMR as a yellow powder, m.p. 85-87°C.

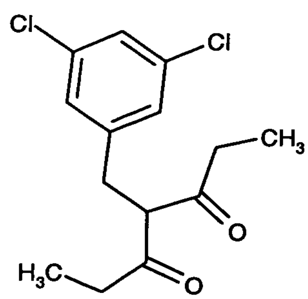
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.02 (s, 6H, enol), 2.15 (s, 6H, diketone), 3.06 (d, 2H, diketone), 3.60 (s, 2H, enol), 3.93 (t, 1H, diketone), 7.00 (s, 2H, enol), 7.03 (s, 2H, diketone), 7.21 (s, 1H, diketone and enol), 16.78 (s, 1H, enol).

LRMS (electrospray): m/z [$M-H^+$] 257.

Microanalysis: Found: C, 55.91; H, 4.72. $C_{12}H_{12}Cl_2O_2$ requires C, 55.62; H, 4.67.

PREPARATION 5

4-(3,5-Dichlorobenzyl)-3,5-heptanedione

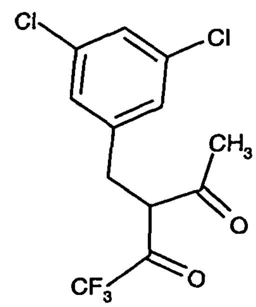


The title compound was prepared by a method similar to that of Preparation 1, Method B using the alkene of Preparation 14 and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (20:1, by volume) then pentane:ethyl acetate (10:1, by volume) to give the title compound as a mixture with its enol tautomer as estimated by ^{1}H-NMR as an orange oil. A small amount (*ca.*10%) of dechlorinated impurities presumably arising from over reduction were detected by ^{1}H-NMR. This over reduction could probably be avoided by using the alternative reduction procedure of Preparation 6.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.00 (m, 6H, diketone and enol), 2.40 (m, 4H, diketone and enol), 3.11 (d, 2H, diketone), 3.64 (d, 2H, enol), 3.97 (t, 1H, diketone), 7.03 (d, 2H), 7.22 (s, 1H), 17.02 (s, 1H, enol).

PREPARATION 6

3-(3,5-Dichlorobenzyl)-1,1,1-trifluoro-2,4-pentanedione



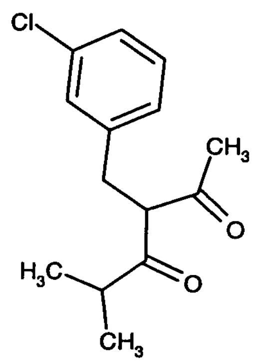
To a solution of a mixture of the alkenes from Preparation 13 (100mg, 0.321mmol) in dichloromethane (3mL) was added diphenylsilane (88.6mg, 0.481mmol) then tetrakis(triphenylphospine)palladium(0) and finally zinc chloride (8mg, 0.06mmol) and the resulting mixture was stirred under nitrogen at room temperature for 3 days. The mixture was applied directly to a silca gel column and purified by flash chromatography eluting with a solvent gradient of dichloromethane:pentane (1:3, by volume) then with dichloromethane:pentane (1:2, by volume) to give the title compound (78mg) as a mixture with its enol tautomer as shown by ^{1}H-NMR as a pale yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = (enol only, signals for diketone not assigned) 2.14 (s, 3H), 3.78 (s, 2H), 7.02 (2, 2H), 7.09 (m, 1H), 16.29 (br. s, 1H).

LRMS (electrospray): m/z [$M-H^+$] 311.

PREPARATION 7

3-(3-Chlorobenzyl)-5-methyl-2,4-hexanedione

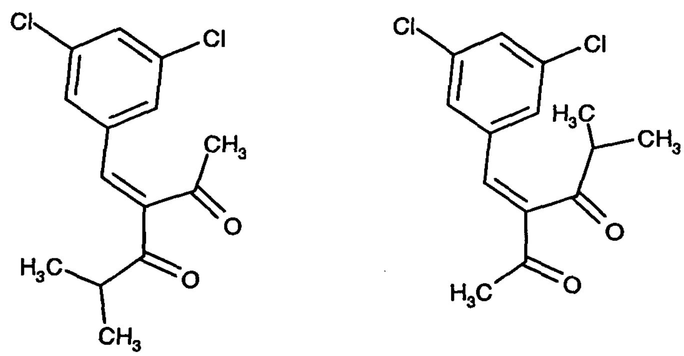


The title compound was prepared by a similar method to that of Preparation 6 using a mixture of the alkenes of Preparation 10, and was purified by flash chromatography eluting with pentane:ethyl acetate (3:1, by volume) and was obtained as a mixture with its enol tautomer as shown by ^{1}H-NMR as a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.97-1.01 (m, 6H, diketone and enol), 2.02 and 2.10 (2s, 2x3H, diketone and enol), 2.53 and 2.66 (2m, 2x1H, diketone and enol), 3.07 (m, 2H, diketone), 3.61 (s, 2H, enol), 4.05 (m, 1H, diketone), 7.08 (m, 4H, diketone and enol).

PREPARATION 8

(3*E*)-3-(3,5-Dichlorobenzylidene)-5-methyl-2,4-hexanedione and (3*Z*)-3-(3,5-dichlorobenzylidene)-5-methyl-2,4-hexanedione



A mixture of 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.,* 1980, 2095-6.) (1.84g, 14.33mmol), 3,5-dichlorobenzaldehyde (2.5g, 14.33mmol), glacial acetic acid (214µL, 3.73mmol), piperidine (29µL, 0.29mmol), dry toluene (10.2mL) and powdered 3Å molecular sieves (100mg) was heated at reflux under nitrogen for 24 hours. A Dean-Stark trap was attached to the reaction and refluxing continued for 3 hours during which time the toluene evaporated from the reaction. The residue was diluted with dichloromethane (80mL) and filtered to remove molecular sieves. The filtrate was washed with water (80mL), dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give the less polar title compound (510.6mg) as a yellow oil.

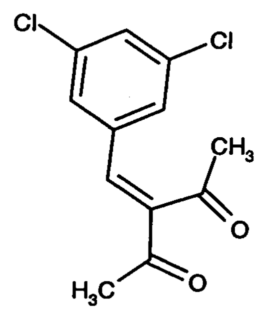
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.19 (d, 6H), 2.29 (s, 3H), 3.19 (heptet, 1H), 7.24 (s, 2H), 7.34 (s, 1H), 7.40 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 302.

Further elution of the same column gave the more polar title compound (993.3mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.05 (d, 6H), 2.40 (s, 3H), 2.58 (heptet, 1H), 7.24 (s, 2H), 7.39 (s, 1H), 7.45 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 302.

PREPARATION 9

3-(3,5-Dichlorobenzylidene)-2,4-pentanedione



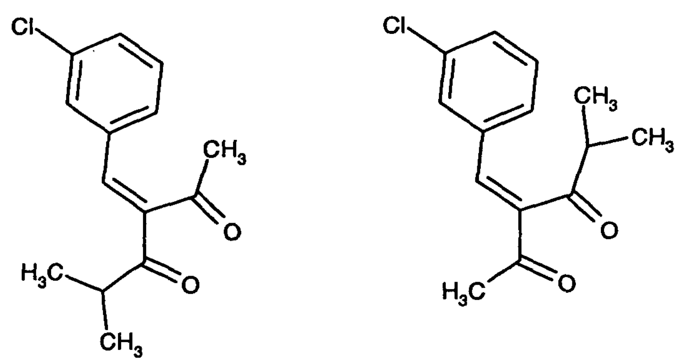
Glacial acetic acid (0.49mL, 8.6mmol) and piperidine (57μL, 0.6mmol) were added to a stirred solution of 2,4-pentanedione (2.86g, 28.6mmol) and 3,5-dichlorobenzaldehyde (5.00g, 28.6mmol) in toluene (25mL) and the mixture was heated at reflux under a Dean-Stark trap for 18 hours. After cooling the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (10:1, by volume) to give the title compound (6.5g) as a red/brown solid, m.p. 85-87°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.22 (s, 3H), 2.39 (s, 3H), 7.21 (s, 2H), 7.26 (s, 1H), 7.35 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 274.

Microanalysis: Found: C, 55.93; H, 3.81. $C_{12}H_{10}Cl_2O_2$ requires C, 56.06; H, 3.92.

PREPARATION 10

(3*E*)-3-(3-Chlorobenzylidene)-5-methyl-2,4-hexanedione and (3*Z*)-3-(3-chlorobenzylidene)-5-methyl-2,4-hexanedione



The title compounds were prepared by a similar method to that of Preparation 9 using 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.*, 1980, 2095-6.) and 3-chlorobenzaldehyde and were obtained as yellow oils.

Less polar isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (d, 6H), 2.24 (s, 3H), 3.18 (m, 1H), 7.30 (m, 6H).

LRMS (thermospray): m/z [MNH_4^+] 268.

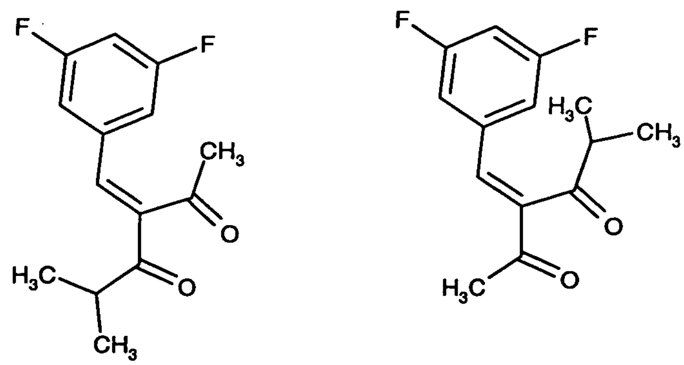
More polar isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.02 (d, 6H), 2.39 (s, 3H), 2.55 (m, 1H), 7.31 (m, 5H), 7.50 (s, 1H).

LRMS (thermospray): m/z [MNH_4^+] 268.

PREPARATION 11

(3*E*)-3-(3,5-Difluorobenzylidene)-5-methyl-2,4-hexanedione and (3*Z*)-3-(3,5-difluorobenzylidene)-5-methyl-2,4-hexanedione



The title compounds were prepared by a similar method to that of Preparation 9 using 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.,* 1980, 2095-6.) and 3,5-difluorobenzaldehyde and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) then pentane:ethyl acetate (10:1, by volume) to give the less polar title compound as a yellow oil.

Less polar isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (d, 6H), 2.27 (s, 3H), 3.19 (heptet, 1H), 6.92 (m, 3H), 7.32 (s,1H).
LRMS (electrospray): m/z [MNH_4^+] 253.

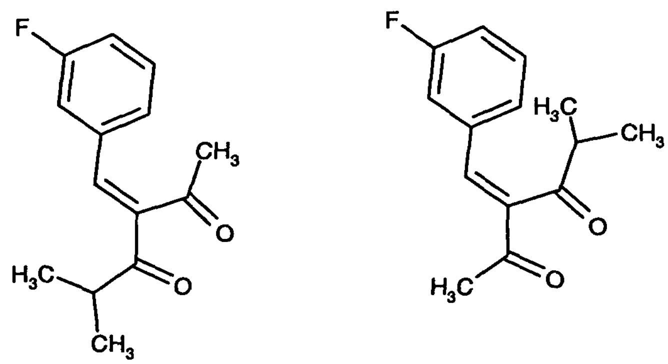
Further elution of the same column gave the more polar title compound as a yellow oil.

More polar isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (d, 6H), 2.40 (s, 3H), 2.56 (heptet, 1H), 6.96 (m, 3H), 7.44 (s, 1H).
LRMS (electrospray): m/z [MNH_4^+] 253.

PREPARATION 12

<u>(3*E*)-3-(3-Fluorobenzylidene)-5-methyl-2,4-hexanedione and (3*Z*)-3-(3-fluorobenzylidene)-5-methyl-2,4-hexanedione</u>



The title compounds were prepared by a similar method to that of Preparation 9 using 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.*, 1980, 2095-6.) and 3-fluorobenzaldehyde and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) then pentane:ethyl acetate (10:1, by volume) to give the less polar title compound as a yellow oil.

Less polar isomer:

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.23 (d, 6H), 2.29 (s, 3H), 3.24 (heptet, 1H), 7.13 (m, 3H), 7.39 (m,1H), 7.44 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 235.

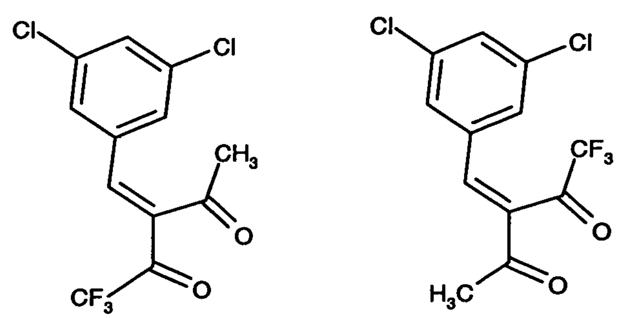
Further elution of the same column gave the more polar title compound as a yellow oil.

More polar isomer:

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.06 (d, 6H), 2.42 (s, 3H), 2.60 (heptet, 1H), 7.11 (m, 3H), 7.35 (m,1H), 7.55 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 235.

PREPARATION 13

<u>(3*E*)-3-(3,5-Dichlorobenzylidene)-1,1,1-trifluoro-2,4-pentanedione and (3*Z*)-3-(3,5-dichlorobenzylidene)-1,1,1-trifluoro-2,4-pentanedione</u>



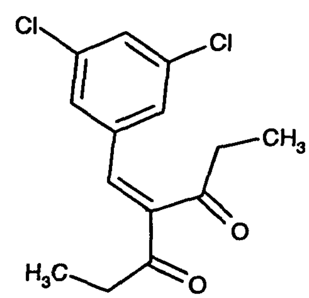
Glacial acetic acid (0.425mL, 7.423mmol) and piperidine (57µL, 0.571mmol) were added to a stirred solution of 1,1,1-trifluoro-2,4-pentanedione (4.40g, 28.55mmol) and 3,5-dichlorobenzaldehyde (5.0g, 28.55mmol) in toluene (20mL) and the mixture was heated at reflux under a Dean-Stark trap for 16h. After cooling the mixture was washed with brine (30mL), dried over magnesium sulphate and concentrated under reduced pressure to give a dark brown oil (9.1g) which was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (10:1, by volume) then pentane:ether (5:1, by volume) then dichloromethane:pentane (1:1, by volume) to give the crude products (4.2g) as a brown oil. The crude products were further purified by

flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:pentane (1:4, by volume) then dichloromethane:pentane (1:3, by volume) to give a mixture of the title compounds (683mg) as shown by thin layer chromatography using dichloromethane:pentane (1:1, by volume) major isomer R_f 0.54, minor isomer R_f 0.17 as a pale yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.49 (s, 3H), 7.23 (s, 2H), 7.46 (s, 1H), 7.66 (s, 1H).
LRMS (electrospray): m/z [MH^+] 328.

PREPARATION 14

4-(3,5-Dichlorobenzylidene)-3,5-heptanedione



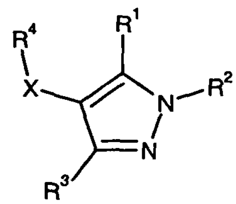
The title compound was prepared by a method similar to that of Preparation 13 using 3,5-heptanedione and was purified by chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give a product which was triturated with pentane to give the title compound as a white solid, m.p. 80-82°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.16 (m, 6H), 2.50 (q, 2H), 2.73 (q, 2H), 7.22 (s, 2H), 7.37 (m, 2H).
LRMS (thermospray): m/z [MH^+] 285.

Microanalysis: Found: C, 58.97; H, 4.95. $C_{14}H_{14}Cl_2O_2$ requires C, 58.98; H, 4.93.

CLAIMS

1. A compound of the formula



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, $-OR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$, $-NR^5CONR^6R^7$, $-NR^5SO_2R^6$ or R^8, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by halo, $-OR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$, $-NR^5CONR^6R^7$, $-NR^5SO_2R^6$ or R^8;

R^2 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl or C-linked R^{12}, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by $-OR^9$, $-CO_2R^9$, $-CO_2NR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{10}$ or R^{12};

R^3 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16}, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16};

R^4 is phenyl or pyridyl, each being optionally substituted by halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy;

R^5, R^6, R^7, R^9, R^{10}, R^{11}, R^{13}, R^{14} and R^{15} are either each H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl or, when two such groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached may represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

R^8, R^{12} and R^{16} are each a five- or six-membered heterocyclic group containing 1 to 4 heteroatoms selected from O, N and S and optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or halo; and

X is $-CH_2-$, -S-, -SO- or $-SO_2-$.

2. A compound of the formula (I), as claimed in claim 1, wherein R^1 is C_1-C_6 alkyl optionally substituted by halo, $-OR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$, $-NR^5CONR^6R^7$, $-NR^5SO_2R^6$ or R^8.

3. A compound of the formula (I), as claimed in claim 2, wherein R^1 is C_1-C_6 alkyl.

4. A compound of the formula (I), as claimed in claim 3, wherein R^1 is C_1-C_3 alkyl.

5. A compound of the formula (I), as claimed in claim 4, wherein R^1 is methyl, ethyl or prop-2-yl.

6. A compound of the formula (I), as claimed in any preceding claim, wherein R^2 is H or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by $-OR^9$, $-CO_2R^9$, $-CO_2NR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{10}$ or R^{12}.

7. A compound of the formula (I), as claimed in claim 6, wherein R^2 is H, methyl or ethyl, said methyl or ethyl being optionally substituted by OR^9 or CO_2R^9.

8. A compound of the formula (I), as claimed in claim 7, wherein R^2 is H, methyl or ethyl, said methyl or ethyl being optionally substituted by OH or $-CO_2CH_2CH_3$.

9. A compound of the formula (I), as claimed in claim 8, wherein R^2 is H, $-CH_2CH_2OH$ or $-CH_2CO_2CH_2CH_3$.

10. A compound of the formula (I), as claimed in any preceding claim, wherein R^3 is C_1-C_6 alkyl optionally substituted by halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16}.

11. A compound of the formula (I), as claimed in claim 10, wherein R^3 is C_1-C_3 alkyl optionally substituted by halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16}.

12. A compound of the formula (I), as claimed in claim 11, wherein R^3 is methyl, ethyl or prop-2-yl, each optionally substituted by halo.

13. A compound of the formula (I), as claimed in claim 12, wherein R^3 is methyl, ethyl, prop-2-yl or trifluoromethyl.

14. A compound of the formula (I), as claimed in any preceding claim, wherein R^4 is phenyl optionally substituted by halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy.

15. A compound of the formula (I), as claimed in claim 14, wherein R^4 is phenyl optionally substituted by halo.

16. A compound of the formula (I), as claimed in claim 15, wherein R^4 is phenyl optionally substituted by chloro or fluoro.

17. A compound of the formula (I), as claimed in claim 16, wherein R^4 is 3-chlorophenyl, 3,5-dichlorophenyl, 3-fluorophenyl, 3,5-difluorophenyl or 4-chlorophenyl.

18. A compound of the formula (I), as claimed in any preceding claim, wherein X is -S- or $-CH_2-$.

19. A compound of the formula (I), as claimed in claim 18, wherein X is $-CH_2-$.

20. A compound of the formula (I), as claimed in claim 1, which is selected from:
2-[4-(3,5-dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-3-ethyl-5-ethyl-1*H*-pyrazol-1-yl]ethanol; and
2-[4-(3,5-dichlorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol.

21. A pharmaceutical composition including a compound of the formula (I), as defined in any preceding claim, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

22. A compound of the formula (I), as defined in any one of claims 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, for use as a medicament.

23. The use of a compound of the formula (I), as defined in any one of claims 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, in the

manufacture of a medicament for the treatment of a disease treatable by the inhibition of reverse transcriptase.

24. The use of a compound of the formula (I), as defined in any one of claims 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment or prevention of a retroviral infection.

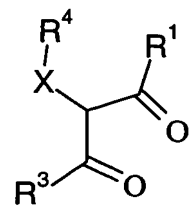
25. The use of a compound of the formula (I), as defined in any one of claims 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment or prevention of AIDS or HIV infection.

26. A method of treatment or prevention of a disorder treatable by the inhibition of reverse transcriptase, comprising the administration of an effective amount of a compound of the formula (I), as defined in any one of claims 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need of such treatment or prevention.

27. A method of treatment or prevention of a retroviral infection, comprising the administration of an effective amount of a compound of the formula (I), as defined in any one of claims 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need of such treatment or prevention.

28. A method of treatment or prevention of AIDS or HIV infection, comprising the administration of an effective amount of a compound of the formula (I), as defined in any one of claims 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need of such treatment or prevention.

29. A process for the preparation of a compound of the formula (I), as defined in claim 1, wherein X is $-CH_2-$ or -S-, which includes the reaction of a compound of the formula

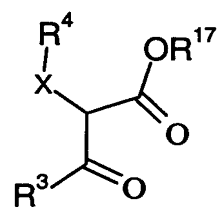


with a compound of the formula

$$H_2NNHR^2 \text{ (V)},$$

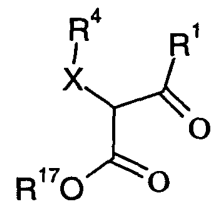
or a salt thereof, optionally followed by the conversion of the compound of the formula (I) to a pharmaceutically acceptable salt or solvate thereof, where R^1, R^2, R^3 and R^4 are as defined for a compound of the formula (I) in claim 1 and X is $-CH_2-$ or -S-.

30. A process for the preparation of a compound of the formula (I), as defined in claim 1, in which R^1 is OH and X is $-CH_2-$ or -S-, which includes the reaction of a compound of the formula



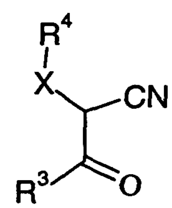
with a compound of the formula (V), as defined in claim 29, or a salt thereof, optionally followed by the conversion of the compound of the formula (I) to a pharmaceutically acceptable salt or solvate thereof, where R^{17} is C_1-C_6 alkyl, R^3 and R^4 are as defined for a compound of the formula (I) in claim 1 and X is $-CH_2-$ or -S-.

31. A process for the preparation of a compound of the formula (I), as defined in claim 1, in which R^3 is OH and X is $-CH_2-$ or -S-, which includes the reaction of a compound of the formula



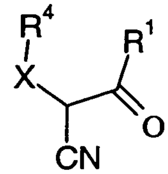
with a compound of the formula (V), as defined in claim 29, or a salt thereof, optionally followed by the conversion of the compound of the formula (I) to a pharmaceutically acceptable salt or solvate thereof, where R^{17} is C_1-C_6 alkyl, R^1 and R^4 are as defined for a compound of the formula (I) in claim 1 and X is $-CH_2-$ or -S-.

32. A process for the preparation of a compound of the formula (I), as defined in claim 1, in which R^1 is NH_2 and X is $-CH_2-$ or -S- which includes the reaction of a compound of the formula



with a compound of the formula (V), as defined in claim 29, or a salt thereof, optionally followed by the conversion of the compound of the formula (I) to a pharmaceutically acceptable salt or solvate thereof, where R^3 and R^4 are as defined for a compound of the formula (I) in claim 1 and X is $-CH_2-$ or -S-.

33. A process for the preparation of a compound of the formula (I), as defined in claim 1, in which R^3 is NH_2 and X is $-CH_2-$ or -S- which includes the reaction of a compound of the formula



with a compound of the formula (V), as defined in claim 29, or a salt thereof, optionally followed by the conversion of the compound of the formula (I) to a pharmaceutically acceptable salt or solvate thereof, where R^1 and R^4 are as defined for a compound of the formula (I) in claim 1 and X is $-CH_2-$ or -S-.